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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(s)
Office Action Summary	10/087,441	PALSSON ET AL.
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) OR THIRTY (30) DAYS,
WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed
  after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any
  earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *16 January 2009*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is
closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16 and 18-74* is/are pending in the application.

    4a) Of the above claim(s) *66-69* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16,18-65 and 70-74* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a) ☐ All b) ☐ Some * c) ☐ None of:

        1. ☐ Certified copies of the priority documents have been received.

        2. ☐ Certified copies of the priority documents have been received in Application No. _____.

        3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage
           application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
    Paper No(s)/Mail Date *1/16/2009*.

4) ☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Comments

In view of the new grounds of rejection set forth below under 35 USC 103, the finality of the last action is withdrawn.

Applicants' request for reconsideration in the communication filed on 17 March 2008 is acknowledged.

Claims 1-16, and 18-74 are pending and claims 1-16, 18-65, and 70-74 are examined in this Office action.

Claims 66-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7 June 2004.

Withdrawn Rejections

ALL of the rejections from the previous Office action are WITHDRAWN in view of the fact that the reference of Hatzimanikatis et al. does not teach use of stoichiometric coefficients to relate substrates to products.

The rejections of the instant Office action are NEWLY applied.

Information Disclosure Statement

The information disclosure statement filed 16 January 2009 has been

considered.

Claim Rejections – 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of
matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the
conditions and requirements of this title.

Claims 34-65 and 70-74 are rejected under 35 U.S.C. 101 because the claimed

invention is directed to non-statutory subject matter.

The method claims of the instant application (instant claims 34-65 and 70-74)

recite a series of steps without a physical transformation. Further, the claims fail to

recite a tie to a specific machine. It is noted that while the result of the calculation is

output to a user, this final step is an insignificant post-solution activity and does not

constitute a significant tie to a specific machine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set
forth in section 102 of this title, if the differences between the subject matter sought to be patented and
the prior art are such that the subject matter as a whole would have been obvious at the time the
invention was made to a person having ordinary skill in the art to which said subject matter pertains.
Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

<u>35 U.S.C. 103 Rejection #1</u>:

Claims 34-42, 44-45, 48-49, 51-63, and 70-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. [AIChE Journal, 1996, volume 42, pages 1277-1292] in view of Varma et al. [Bio/Technology. Volume 12, 1994, pages 994-998].

Claim 34 is drawn to a method for determine a systemic property of a biochemical reaction network, comprising:

--providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction;

--providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction;

--providing a condition-dependent value to said variable constraint;

--providing an objective function;

--determining at least one flux distribution that minimizes or maximizes said objective function when said constraint is applied to said data structure, wherein said at least one flux distribution is determinative of a systemic property of said biochemical reaction network; and

--providing said systemic property of said biochemical reaction network to a user.

Claim 71 is drawn to a method for determining a systemic property of a biochemical reaction network at a first and a second time comprising:

--providing a data structure relating a plurality of reactant to a plurality of reactions of a biochemical reaction network wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction;

--providing a constraint for said plurality of reactions, wherein said constraint set comprised a variable constraint for said regulated reaction;

--providing a condition-dependent value to said variable constraint;

--providing an objective function;

--determining at least one flux distribution at a first time that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby determining a systemic property of said biochemical reaction network at said first time;

--modifying said value to said variable constraint;

--repeating step (e) wherein said at least one flux distribution is determined at a second time, thereby determining a systemic property of said biochemical reaction network at a second time; and

--providing said systemic property of said biochemical reaction network to a user at said first, second, or first and second time.

These independent claims have the same three core concepts: 1. providing of a data structure containing a system of reactions where a subset of the reactions is regulated, 2. providing a constraint set under which the reactions are operated (of which a subset of the constraints are variable constraints), 3. optimizing an objective function in order to determine a systemic property resulting from the system as a result of a flux distribution analysis. The results are provided to a user.

Claim 34 has the extra limitation of a condition dependent constraint.

Claim 71 has the extra limitation of a condition dependent constraint and the further limitation of iteratively modifying the variable constraint.

The article of Hatzimanikatis et al. studies analysis and design of metabolic

reaction networks via mixed integer linear optimization.

The first several sentences of the abstract of Hatzimanikatis et al. state:

> Improvements in bioprocess performance can be achieved by genetic modifications of metabolic
> control structures. A novel optimization problem helps quantitative understanding and rational
> metabolic engineering of metabolic reaction pathways.

Hatzimanikatis et al. continues in the abstract to describe that the problem to be

solved is finding the optimal regulatory structure for maximization of phenylalanine

selectivity in the microbial aromatic synthesis pathway.

An illustration of the reaction pathway studies on Hatzimanikatis et al. is shown in

Figure 1 on page 1283 where several of the reactions are regulated (i.e. dotted lines in

the Figure indicate regulatory reactions).

The system is mathematically described on page 1279 in Equation 1 and the

paragraph bridging the first and second columns, which states:

> Consider a metabolic system consisting of n metabolites and m enzymatically-catalyzed
> reactions. We are in [sic] interested in studying how modifications of the expression levels and of
> the properties of the enzymes that catalyze these reactions affect metabolic functions of the
> system, such as metabolite concentrations, fluxes, and specific growth rate.

Consequently, flux distributions through this amino acid synthesis pathway are

studied.

Constraints are described on pages 1282-1283 of Hatzimanikatis et al. The

constraints include mass balances (non variable constraints), constraints based on

continuous variables (variable constraints), and logical constraints based on the

presence of certain regulatory loops (binary variable constraints). Some of the

constraints (i.e. the binary constraints) are condition dependent on the presence of

certain regulated reactions in the network. The values of the constraints are

conditionally dependent on which of the eight pathways of solutions in Figure 2 on page 1284 of Hatzimanikatis et al. is selected.

The objective function is listed in Equation 12 on page 1281 of Hatzimanikatis et al. The goal of the study of Hatzimanikatis et al. is to maximize and minimize this function.

Table 1 on page 1285 of Hatzimanikatis et al. shows the solution for the continuous variables for six iterations in which variable functions and constraints are modified (i.e. optimized). Table 1 is also provides the results of the calculation to a user.

Hatzimanikatis et al. does not teach a data structure or database comprising reactions wherein the reactants and products are identified and are related or linked to a stoichiometric coefficient.

The article of Varma et al. studies metabolic flux balancing.

Specifically, equation 1 on page 994 and Figure 1 on page 995 of Varma et al. teach use of stoichiometric matrices to relate reactants to products in metabolic processes.

Claim 35 is further limiting in that said variable constraint is dependent upon the outcome of at least one reaction.

Claim 36 is further limiting in that said variable constraint is dependent upon the outcome of at least one regulatory event.

Claim 37 is further limiting in that the variable constraint is dependent on time.

Claim 38 is further limiting wherein said variable constraint is dependent upon the presence of a biochemical network participant.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates the eight best solution pathways for solving the optimization problem. Each of these solutions is interpreted to be calculated at a different time. Each pathway has a different set of reactions and regulatory events based on the calculation of different logical constraints (binary variable constraint that indicate the existence or nonexistence of various regulatory loops- see bottom of second column of page 1282).

Claim 39 is further limiting wherein the participant is a substrate or product.

The reactions in Figure 1 of Hatzimanikatis et al. list substrates and products.

Claim 40 is further limiting wherein the said biochemical reaction network comprises metabolic reactions.

The pathway described in Figure 1 of Hatzimanikatis et al. is a metabolic pathway.

Claim 41 is further limiting comprising a regulatory data structure, wherein said variable constraint is dependent upon an outcome of a regulatory event represented by a data structure.

Logical constraints are binary variable constraints that indicate the existence or

nonexistence of various regulatory loops- see bottom of second column of page 1282 of

Hatzimanikatis et al.

Claim 42 is further limiting wherein one of the regulatory events can be inhibition

or activation of a protein.

Hatzimanikatis et al. teaches activation and inhibition of enzymes in metabolism

in the third paragraph from the bottom in column 2 on page 1280 as examples of

regulation events that affect the studied metabolic network.

Claim 44 is further limiting wherein said biochemical network and said regulatory

data structure represent reactions or events that occur in a single cell.

The last line of page 1277 of Hatzimanikatis et al. indicates that the pathway

occurs in a cell.

Claim 45 is further limiting wherein the regulatory event comprises a regulatory

reaction.

The regulatory events in Hatzimanikatis et al. are the regulatory reactions

described in Hatzimanikatis et al. (i.e. Figure 1 of Hatzimanikatis et al.)

Claim 48 is further limiting wherein there is a constraint function that correlates

an outcome of a variable event with a variable constraint.

These functions are given on page 1283 of Hatzimanikatis et al. in Equations 22-26.

Claim 49 is further limiting wherein the constraint is binary.

The logical constraints of Hatzimanikatis et al. are binary constraints indicating the presence or absence of certain regulatory events in the synthesis pathway.

Claim 51 is further limiting wherein said constraint function correlates a first set of outcomes of said regulatory data structure with a first binary value and a second set of outcomes of said regulatory data structure with a second binary value.

Claim 52 is further limiting wherein said constraint function correlates a set of outcomes of said regulatory data structure with a single integer value.

The logical constraints in the bottom of the second column of page 1282 are binary variables indicating the presence of certain outcomes (i.e. presence) of certain regulatory reactions. Binary variables have single integer values.

Claim 53 is further limiting wherein the commands comprise an optimization problem. Claim 54 is further limiting wherein the optimization is linear or nonlinear optimization.

The objective of the study of Hatzimanikatis et al. is to use mixed-integer linear optimization to analyze a metabolic reaction (i.e. title). In doing so, flux distributions are calculated between reactions (i.e. see equation 1 on page 1279). Consequently, the

type of optimization studied in Hatzimanikatis et al. is mixed integer LINEAR

OPTIMIZATION, as taught in the title and throughout the article.

Claim 55 is further limiting comprising a step of modifying said data structure or

said constraint set, or both.

Claim 63 is further limiting wherein the constraint function is binary.

Figure 2 of Hatzimanikatis et al. illustrates eight modifications of the data

structure. The presence of a regulatory reaction is based on the result of a binary

constraint function indicating its existence.

Claim 56 is further limiting wherein said data structure comprises a set of linear

algebraic equations.

Claim 57 is further limiting wherein said data comprises a matrix.

The equations of Hatzimanikatis et al. (i.e. equations 6-7 on page 1280 of

Hatzimanikatis et al.) are examples of linear algebraic equations with relevant matrices.

Claim 58 is further limiting by demonstrating flux distributions as a flux

distribution map.

Figure 1 of Hatzimanikatis et al. lists a flux distribution map with each member of

the network being annotated with an abbreviation. Each member of the pathway is

assigned to a different compartment within the Figure of Hatzimanikatis et al.

Claim 59 is further limiting wherein a specific listing of biochemical processes lists biosynthesis of an amino acid as a possible result of the network of reactions.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 60 is further limiting wherein a systemic property is chosen from a given list including production of an amino acid.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 61 is further limiting wherein the systemic property comprises degradation.

The last full paragraph of column 2 on page 994 of Varma et al. describes that the mass balancing techniques are equally applicable to degradation as well as formation of metabolites.

Claim 62 is further limiting wherein there are a plurality of regulated reactions and variable constraints. Claim 63 is further limiting wherein the constraint function is binary.

Figures 1-3 of Hatzimanikatis et al. illustrate a plurality of regulated reactions governed by a plurality of variable constraints.

Figure 2 of Hatzimanikatis et al. illustrates eight modifications of the data structure. The presence of a regulatory reaction is based on the result of a binary constraint function indicating its existence.

Claim 70 is further limiting wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise boundary values.

Claim 72 is further limiting wherein said value is modified based on said flux distribution at said first time.

Claim 73 is further limiting wherein said value is modified based on a change in an environmental condition.

Claim 74 is further limiting wherein steps of claim 71 for a specified number of time points.

Equations 14 and 15 on page 1282 of Hatzimanikatis et al. illustrates boundary constraints intended to limit the pathway to physiological conditions. The pathways are consequently modified in such a way to function under physiological conditions. The multiple iterations in Table 1 of Hatzimanikatis et al. are interpreted to be conducted at multiple time points.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the flux distribution and reaction optimization of Hatzimanikatis et al. by use of the stoichiometric analyses of Varma et al. wherein the motivation would have been that the stoichiometric matrices of Varma et al. are

necessary to provide an accurate mass balance over the metabolic system [see last full

paragraph of column 2 on page 994 of Varma et al.]

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they

are not persuasive.

Applicant has a main argument regarding this Hatzimanikatis et al. which is

reiterated from the previous Remarks of 17 March 2008.

The argument is that the intended invention and the prior art do not coincide with

solving the same intended problem. Applicant states that the instant invention is not

drawn to determining and optimizing the "regulatory superstructure" of a set of reactions

governing a process, but rather, it is drawn to optimizing and designing a set of optimal

values of networks. Applicant states this succinctly on page 15 of the Remarks, wherein

applicant states:

> Thus, it is clear that Hatzimanikatis describes designing regulatory structures, including regulatory
> loops that do not naturally occur in a metabolic pathway.

This argument is not persuasive because the instant set of claims is broad

enough to encompass both optimizing and designing a set of reaction networks (as in

Hatzimanikatis et al.) as well as determining a systemic property of an existent and

specific biological network (as is what applicant is arguing). The instant claims are not

limited to recite "optimizing" and/or "designing" a set of optimal values of networks.

Rather, claim 34 recites minimizing OR maximizing an objective function of a flux

distribution. This MAY result in "optimization" of the flux distribution, and hence the

reaction network, but not necessarily. Claim 53 recites that the flux distribution is "determined by optimization," but this is not a step of determining optimal "values" for the entirety of a network. Further, Hatzimanikatis et al. teaches optimizing in the title, conclusion, and throughout the article. In addition, the biological reaction networks of the claims are not limited to be a specific, existent network.

35 U.S.C. 103 Rejection #2:

Claims 1-12, 14-15, 18-28, 30, 32-33, 43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al, in view of Varma et al. as applied to claims 34-42, 44-45, 48-49, 51-63, and 70-74 above, in further view of Grewal et al. [Protein Engineering, volume 7, 1994, pages 205-211].

Claim 1 is drawn to a computer readable medium or media having stored thereon instructions to perform the following steps:

--providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as the product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction;

--providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction

--determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data structure, wherein

said at least one flux distribution determines a systemic property of said biochemical

reaction network, and wherein said systemic property is dependent upon the flux

through said regulated reaction, and

--providing information resulting from the method to a user.

As discussed in the prior art rejection above, the articles of Hatzimanikatis et al.

and Varma et al. study analysis and design of metabolic reaction networks via mixed

integer linear optimization.

However, Hatzimanikatis et al. and Varma et al. do not describe the automated

aspects of the instant set of claims.

The article of Grewal et al. studies computer modeling of the interactions

between proteins involved in metabolism. Specifically, the last full paragraph in column

2 on page 205 of Grewal et al. describes use of the ALIGN program in the PIR software

package run on a VAXII computer.

Claim 2 is further limiting in that said variable constraint is dependent upon the

outcome of at least one reaction.

Claim 3 is further limiting in that said variable constraint is dependent upon the

outcome of at least one regulatory event.

Claim 4 is further limiting in that the variable constraint is dependent on time.

Claim 5 is further limiting wherein said variable constraint is dependent upon the

presence of a biochemical network participant.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates the eight best solution

pathways for solving the optimization problem. Each of these solutions is interpreted to

be calculated at a different time. Each pathway has a different set of reactions and

regulatory events based on the calculation of different logical constraints (binary

variable constraint that indicate the existence or nonexistence of various regulatory

loops- see bottom of second column of page 1282).

Claim 6 is further limiting wherein the participant is a substrate or product.

The reactions in Figure 1 of Hatzimanikatis et al. list substrates and products.

Claim 7 is further limiting wherein the said biochemical reaction network

comprises metabolic reactions.

The pathway described in Figure 1 of Hatzimanikatis et al. is a metabolic

pathway.

Claim 8 is further limiting comprising a regulatory data structure, wherein said

variable constraint is dependent upon an outcome of a regulatory event represented by

a data structure.

Logical constraints are binary variable constraints that indicate the existence or

nonexistence of various regulatory loops- see bottom of second column of page 1282 of

Hatzimanikatis et al.

Claim 9 is further limiting wherein one of the regulatory events can be inhibition or activation of a protein.

Hatzimanikatis et al. teaches activation and inhibition of in metabolism in the third paragraph from the bottom in column 2 on page 1280 as examples of regulation events that affect the studied metabolic network.

Claims 10 and 43 are further limiting wherein the regulatory event is due to a signal transduction pathway.

The second paragraph of the Introduction of Grewal et al. on page 205 teaches the application of ligand-receptor interactions in signal transduction pathways.

Claim 11 is further limiting wherein said biochemical network and said regulatory data structure represent reactions or events that occur in a single cell.

The last line of page 1277 of Hatzimanikatis et al. indicates that the pathway occurs in a cell.

Claims 12 and 46 are further limiting wherein said biochemical reaction network represents reactions that occur in a first cell in a population of cells and said regulatory data structure events occur in a second cell.

The second paragraph of the Introduction of Grewal et al. on page 205 teaches the application of ligand-receptor interactions in signal transduction pathways. The first

paragraph of the introduction suggests that signal transduction as a result of this study

can occur extracellularly (i.e. between two cells).

Claim 14 is further limiting wherein there is a constraint function that correlates

an outcome of a variable event with a variable constraint.

These functions are given on page 1283 of Hatzimanikatis et al. in Equations 22-

26.

Claim 15 is further limiting wherein the constraint is binary.

The logical constraints of Hatzimanikatis et al. are binary constraints indicating

the presence or absence of certain regulatory events in the synthesis pathway.

Claim 18 is further limiting comprising a range of feasible flux distributions.

Claim 19 is further limiting wherein the commands comprise an optimization

problem. Claim 20 is further limiting wherein the optimization is linear or nonlinear

optimization.

The objective of the study of Hatzimanikatis et al. is to use mixed-integer linear

optimization to analyze a metabolic reaction (i.e. title). In doing so, flux distributions are

calculated between reactions (i.e. see equation 1 on page 1279). Hatzimanikatis et al.

teaches optimization, for example, in the title and conclusion of the study.

Claim 21 is further limiting that there is a user interface capable of sending at

least one command for modifying said data structure. Claim 22 is further limiting

wherein said user interface further comprises links which a user may select to access additional information relating to said plurality of reactions.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates such a user interface with visual links to each of the eight regulatory pathways. Each of the eight pathways is based on different optimization constraints resulting in different reaction networks.

Claim 23 is further limiting wherein said data structure comprises a set of linear algebraic equations.

Claim 24 is further limiting wherein said data comprises a matrix.

The equations of Hatzimanikatis et al. (i.e. equations 6-7 on page 1280 of Hatzimanikatis et al.) are examples of linear algebraic equations with relevant matrices.

Claim 25 is further limiting by demonstrating flux distributions as a flux distribution map.

Claim 26 is further limiting by annotating reactants and products.

Claim 27 is further limiting wherein a reactant is assigned a compartment.

Claim 28 is further limiting wherein a reactant is assigned to a compartment and another reactant is assigned to a different compartment.

Figure 1 of Hatzimanikatis et al. lists a flux distribution map with each member of the network being annotated with an abbreviation. Each member of the pathway is assigned to a different compartment within the Figure of Hatzimanikatis et al.

Claim 30 is further limiting wherein the annotation comprises a confidence limit for occurrence of the reaction.

Column 1 on page 1286 of Hatzimanikatis et al. demonstrates selecting a reaction scheme with 95 % selectivity by using three separate enzymes to conduct the reaction.

Claim 32 is further limiting wherein a specific listing of biochemical processes lists biosynthesis of an amino acid as a possible result of the network of reactions.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 33 is further limiting wherein there are a plurality of regulated reactions and variable constraints.

Figures 1-3 of Hatzimanikatis et al. illustrate a plurality of regulated reactions governed by a plurality of variable constraints.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the flux distribution and reaction optimization of Hatzimanikatis et al. and Varma et al. by use of the computerized embodiments of Grewal et al. wherein the motivation would have been that automation result in quicker, more expedient, and accurate results [see for example, last full paragraph of column 2 on page 205 of Grewal et al.]. It would have been further obvious to incorporate the

multi-cellular signal transduction method of Grewal et al. in the method of

Hatzimanikatis et al. and Varma et al. where the motivation would have been to better

design peptide antagonists for therapeutic applications such as through the better

understanding of hCG-receptor interaction by three dimensional mapping, as taught by

Grewal et al. on page 211.

Response to Arguments:

    Applicant's arguments filed 16 January 2009 have been fully considered but they

are not persuasive.

    Applicant's arguments concerning the reference of Hatzimanikatis et al. have

been addressed above and are reiterated.

35 U.S.C. 103 Rejection #3:

    Claims 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Hatzimanikatis et al. in view of Varma et al. as applied to claims 34-42, 44-45, 48-49,

51-63, and 70-74 above, and further in view of Liao et al. [Biotechnology and

Bioengineering, volume 52, 1996, pages 129-140].

    Claim 64 is further limiting comprising a gene database relating one or more

reactions in said data structure with one or more open reading frames or proteins in a

particular organism.

    Claim 65 is further limiting comprising identifying an open reading frame that

encodes a protein that performs a plurality of reactions.

Hatzimanikatis et al. and Varma et al. make obvious a method of using linear
optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al. and Varma et al. do not teach use of open reading frames
and gene databases.

The article of Liao et al. investigates pathway analysis, engineering, and
physiological considerations for redirecting central metabolism.

Figure 3 on page 132 of Liao et al. illustrates a data base of relevant expression
from different mutant genes with open reading frames expressing the necessary
proteins listed perform the metabolic pathways of Liao et al. in order to produce
glucose.

The sentences bridging columns 1 and 2 on page 137 of Liao et al. state:

> We have presented evidence suggesting that some of these metabolites serve as an internal
> signal in regulating glucose transport, heat shock response, and nitrogen regulation.

Consequently, the metabolites associated with the genes play a significant role in
regulating biologically important responses.

It would have been obvious to someone of ordinary skill in the art at the time of
the instant invention to modify the reaction optimization of Hatzimanikatis et al. and
Varma et al. by incorporating the genetic analyses of the metabolic pathways of glucose
as taught by Liao et al. where the motivation would have been a better understanding of
an internal method of regulating biological responses such as glucose transport, heat
shock response, and nitrogen regulation as taught by Liao et al. on page 137.

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, every other rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

35 U.S.C. 103 Rejection #4:

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. in view of in view of Varma et al. in view of Grewal et al. as applied to claims 1-12, 14-15, 18-28, 30, 32-33, 34-46, 48-49, 51-63, and 70-74 above, and further in view of Liao et al. [Biotechnology and Bioengineering, volume 52, 1996, pages 129-140].

Claim 31 is further limiting comprising a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins in a particular organism.

Hatzimanikatis et al., Varma et al. and Grewal et al. make obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al. and Grewal et al. do not teach use of open reading frames and gene databases.

The article of Liao et al. investigates pathway analysis, engineering, and physiological considerations for redirecting central metabolism.

Figure 3 on page 132 of Liao et al. illustrates a data base of relevant expression from different mutant genes with open reading frames expressing the necessary proteins listed perform the metabolic pathways of Liao et al. in order to produce glucose.

The sentences bridging columns 1 and 2 on page 137 of Liao et al. state:

We have presented evidence suggesting that some of these metabolites serve as an internal signal in regulating glucose transport, heat shock response, and nitrogen regulation.

Consequently, the metabolites associated with the genes play a significant role in regulating biologically important responses.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the automated reaction optimization of Hatzimanikatis et al., Varma et al. and Grewal et al., by incorporating the genetic analyses of the metabolic pathways of glucose as taught by Liao et al. where the motivation would have been a better understanding of an internal method of regulating biological responses such as glucose transport, heat shock response, and nitrogen regulation as taught by Liao et al. on page 137.

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, every other rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

35 U.S.C. 103 Rejection #5:

Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over

Hatzimanikatis et al. in view of Varma et al. as applied to claims 34-42, 44-45, 48-49,

51-63, and 70-74 above, and further in view of Kim et al. [US 2002/00087275 A1; filed

31 July 2001].

Claim 50 is further limiting by incorporating Boolean operators into the reaction

pathway.

Hatzimanikatis et al. and Varma et al. make obvious a method of using linear

optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al. and Varma et al. do not teach usage of Boolean analysis in

the reaction pathways.

The study of Kim et al. studies visualization and manipulation of biomolecular

relationships using graph operators. Figure 1 of Kim et al. illustrates such a graph

theory. Specifically, Paragraph [0097] describes use of Boolean variables when

examining the reaction network.

This analysis of Kim et al. allows for computational algorithms for representing

and analyzing large and heterogeneous molecular biological data (see paragraph

[0002]). The last sentences of paragraph [0010] of Kim et al. explain a disadvantage of

the prior art improved upon in Kim et al.

> However the computation of these [prior art] systems were carried out at the database level by
> querying a database for all potential consecutive binary gene pairs, and subsequently, integrating
> them into pathways.... More complex analyses such as comparing disparate data sets, exploring
> gene network structures, and inferring pathways and gene functions, are either beyond the
> capacity of these systems or computationally too expensive to perform.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the reaction optimization of Hatzimanikatis et al. and Varma et al, by incorporating the genetic graphing algorithms taught by Kim et al. where the motivation would have been a better understanding of complex metabolic networks, as described in paragraphs [0002] and [0010] of Kim et al.

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, every other rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

35 U.S.C. 103 Rejection #6:

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to claims 1-12, 14-15, 18-28, 30, 32-33, 34-46, 48-49, 51-63, and 70-74, above, and further in view of Kim et al. [US 2002/00087275 A1; filed 31 July 2001].

Claim 16 is further limiting by incorporating Boolean operators into the reaction pathway.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach usage of Boolean analysis in the reaction pathways.

The study of Kim et al. studies visualization and manipulation of biomolecular relationships using graph operators. Figure 1 of Kim et al. illustrates such a graph theory. Specifically, Paragraph [0097] describes use of Boolean variables when examining the reaction network.

This analysis of Kim et al. allows for computational algorithms for representing and analyzing large and heterogeneous molecular biological data (see paragraph [0002]). The last sentences of paragraph [0010] of Kim et al. explain a disadvantage of the prior art improved upon in Kim et al.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the reaction optimization of Hatzimanikatis et al., Varma et al. and Grewal et al., by incorporating the genetic graphing algorithms taught by Kim et al. where the motivation would have been a better understanding of complex metabolic networks, as described in paragraphs [0002] and [0010] of Kim et al.

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, every other rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

35 U.S.C. 103 Rejection #7:

Claims 13 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to

claims 34-42, 44-45, 48-49, 51-63, and 70-74 above, and further in view of Vissing et al.

[Neurology, 1996, volume 47, pages 766-771].

Claims 13 and 47 are further limiting in that the events occur in a multicellular

organism.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious an automated

method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach regulated

reaction networks in multicellular organisms.

The study of Vissing et al. examines the sources of enhanced glucose production

during exercise in humans with blocked glycolysis caused by muscle

phosphofructokinase deficiency.

The purpose of understanding this phenomenon is relevant for better

understanding of diseases involving altered glucose production during glycolysis (i.e.

McArdle's disease in the paragraph bridging columns 1 and 2 on page 766).

It would have been obvious to someone of ordinary skill in the art at the time of

the instant invention to modify the reaction optimization of Hatzimanikatis et al., Varma

et al. and Grewal et al., by incorporating the metabolic pathway of glycolysis in humans

of Vissing et al. where the motivation would have been a better understanding of

diseases affected by abnormal glycolysis in multicellular organisms, as taught on page

766 of Vissing et al.

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they

are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, every

other rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not

deficient, this obviousness prior art rejection is not deficient.

35 U.S.C. 103 Rejection #8:

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over

Hatzimanikatis et al. in view of Varma et al. in view of Grewal et al. as applied to claims

1-12, 14-15, 18-28, 30, 32-33, 34-46, 48-49, 51-63, and 70-74 above, and further in

view of Callis [The Plant Cell, volume 7, 1995, pages 845-857].

Claim 29 is further limiting wherein annotation comprises assignment of an open

reading frame to a corresponding protein.

Hatzimanikatis et al., Varma et al., and Grewal et al. make obvious a method of

using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al., Varma et al., and Grewal et al. do not teach metabolism of

proteins.

The article of Callis studies the regulation of protein degradation. Specifically, the paragraph bridging columns 1 and 2 on page 850 demonstrates assignment of an open reading frame encoded by cDNA consistent with specific peptides.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the automated reaction optimization of Hatzimanikatis et al., Varma et al. and Grewal et al., by assigning open reading frames to specific proteins where the motivation would have been that such an assignment facilitates mapping between DNA and proteins [see paragraph bridging columns 1 and 2 on page 850 of Callis].

Response to Arguments:

Applicant's arguments filed 16 January 2009 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, every other rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61

(November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)).

The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Russell Negin, whose telephone number is (571) 272-

1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571)

272-0720.

Information regarding the status of the application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center

(EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin
31 January 2009

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631